REMARKS

Claims 43-51 were pending in the application. Claims 52-58 have been added. Accordingly, claims 43-58 will be pending in the application. In addition, the specification has been amended throughout to insert sequence identifiers for the nucleotide/amino acid sequences recited therein.

Claims 52-58 have been substantially copied from U.S. Patent Number 5,691,188 by Pausch et al., filed on February 14, 1994 and issued on November 25, 1997. Claims 52-58 essentially correspond to claims 17-23 of the '188 patent. Applicants note that claim 43 of the instant application recites "heterologous ***G-protein*** coupled receptor" (emphasis added) whereas claim 1 of the '188 patent recites "heterologous ***protein*** coupled receptor" (emphasis added). Applicants point out, however, that the file history of the '188 patent indicates that claim 1 of the '188 patent should read "G-protein" (*i.e.*, claim 1 of the '188 patent recites "protein" merely due to an error in the printing of the patent). Additionally, Applicants note that claims 43, 47, 49 and 52 of the instant application recite "svg1" whereas the corresponding claims of the '188 patent (claims 1, 12, 14 and 17) recite "sgv1." Applicants submit that the spelling "sgv1" in the '188 patent is a typographical error and that "svg1" and "sgv1" are the same gene.

Support for the new claims can be found in the instant specification and claims as originally filed and/or previously pending, as well as in the applications to which the instant application claims priority. In particular, support for the new claims can be found in parent application USSN 08/041,431, filed on March 31, 1993 (approximately 11 months before the February 14, 1994 filing date of the '188 patent), as outlined in table form below:

52. (New) The yeast cell of claim 50 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1,	page 10, lines 9-13, page 11, lines 23-24 and page 21, lines 27-31
ste2, and ste3.	page 16, lines 22-24, page 22, lines 1-2 and page 23, lines 1-10
53. (New) The yeast cell of claim 52 further comprising a mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest.	page 9, line 33 through page 10, line 1 and page 20, lines 5-12
54. (New) The yeast cell of claims 43 and 50 wherein the reporter gene is selected from the group consisting of HIS3,	page 10, lines 3-5; page 11, line 25; and page 18, lines 13-17
URA3, LYS2, CAN1, and LacZ, and the pheromone responsive promoter is FUS1.	page 19, line 3 through page 20, line 17, page 22, lines 10-21 and page 23, lines 17-19
55. (New) The yeast cell of claim 54 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.	page 9, line 33 through page 10, line 1, page 11, lines 23-24, and page 20, lines 10-12
56. (New) The yeast cell of claim 54 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.	page 9, line 33 through page 10, line 1 and page 20, lines 5-12
57. (New) The yeast cell of claims 43, 44, 45, or 50 further comprising a heterologous Gα subunit.	page 16, line 33 through page 17, line 5

58. (New) The heterologous G protein coupled receptor gene of claims 43, 44, 45, or 50 which encodes a receptor selected from the group consisting of a β 2 adrenergic receptor, an α-2 adrenergic receptor , a 5HT-1A receptor, a muscarinic acetylcholine receptor, a growth hormone releasing factor receptor and a somatostatin receptor.	page 15, lines 3-8 and pages 39-42

No new matter has been added. For the Examiner's convenience, the claims that will be pending upon entry of the amendments presented herein are attached hereto as Appendix A.

Objection to the Specification

The specification is objected to because it does not refer to a particular sequence identifier wherever reference is made to a particular sequence, and because a paper copy of the sequence listing is absent.

Applicants have amended the specification to make reference to a sequence identifier as requested by the Office Action. Furthermore, Applicants request that the objection pertaining to the paper copy of the sequence listing be withdrawn. Pursuant to 37 CFR 1.821(e) the computer readable form of the sequence listing for the above-referenced application (Serial No. 09/286,166) is to be identical with the computer readable form of application Serial No. 08/461,383, filed on June 5, 1995. In addition, pursuant to 37 CFR 1.821(f), the content of the paper copy of the sequence listing for the above-referenced application and the computer readable form of the application serial No. 08/461,383 are the same. Applicants submit herewith a copy of the Divisional-Continuation Application Transmittal Form which indicates that the United States Patent and Trademark Office was authorized to use the computer readable form of application

Serial No. 08/461,383 in lieu of filing a duplicate computer readable form or a paper copy of the sequence listing in the above-identified application.

Claim Rejections - Double Patenting

Rejection of Claims 43-51 Under Double Patenting

Claims 43-51 are rejected "under the judicially created doctrine of obviousness-type double patenting". The Office Action indicates that "[a] timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b)".

Applicants make no comment at this time as to the propriety of the obviousness-type double patenting rejection, and will consider the rejection and the filing of a terminal disclaimer upon an indication from the Examiner that the application is otherwise in condition for allowance.

Claim Rejections - 35 U.S.C. §103

Rejection of Claims 43, 44, 45, 47, 50, and 51 Under 35 U.S.C. §103(a)

Claims 43, 44, 45, 47, 50, and 51 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,284,746 to Sledziewski *et al.* in view of Kang *et al.* (1990) *Mol. Cell. Biol.* 10:2582-2590.

The Office Action, at Section 8, page 5, alleges that it would have been

> "obvious to use hybrid Gαi proteins instead of hybrid G-protein receptors in the assay disclosed in U.S. Patent No. 5284746. The motivation to do so was provided by Kang et al. (supra) who stated that portions of mammalian Gα proteins (Gαi) which bind to mammalian receptors but do not interact with yeast βγ subunits

could be made to do so by expressing them as hybrid proteins containing yeast sequences (See table 2)".

Applicants respectfully traverse this rejection and assert that the cited combination of references fails to establish a *prima facie* showing of obviousness.

The invention, as recited in claim 43, is directed to a transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, with each of the genes being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein. Claims 44, 45, 47, 50 and 51 depend from claim 43. The "hybrid Gα protein" recited in claim 43 comprises the receptor-associated Gα of which one or more segments are replaced with the corresponding endogenous yeast Gα segments, thereby forming a chimeric Gα subunit (instant specification, page 46, lines 8-12). This chimeric Gα subunit will interact with the exogenous receptor (*i.e.*, the heterologous G protein-coupled receptor) and the yeast Gβγ subunit, thereby permitting signal transduction (instant specification, page 46, lines 15-17).

U.S. Patent No. 5,284,746 discloses yeast cells transformed with DNA constructs that encode hybrid G-protein coupled receptors, and methods using the yeast cells so transformed to detect the presence of a ligand in a test substance. The publication neither teaches nor suggests the hybrid Gα proteins of the instant invention. Indeed, the exclusive focus of U.S. Patent No. 5,284,746 is hybrid ***G-protein-coupled receptors***. Applicants submit that one of ordinary skill in the art would certainly not equate hybrid G-protein-coupled receptors with chimeric Gα proteins. Furthermore, the Office Action admits, at page 4, last paragraph, that U.S. Patent No. 5,284,746 does not teach a hybrid Gα protein comprising yeast Gα nor an otherwise heterologous Gα protein.

To establish a *prima facie* case of obviousness "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to

one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." See M.P.E.P. §2143. Applicants submit that the claimed invention is non-obvious over the art of record because, at a minimum, one of ordinary skill in the art would have no motivation to combine the references in the manner suggested in the Office Action, and even if one were to so combine the cited references, there would be no reasonable expectation of success.

The Kang *et al.* reference discloses the preparation of yeast Scg1 and mammalian Gα hybrids, and yeast cells transformed with the hybrids in an effort to determine if the hybrids complement the endogenous yeast pheromone responsive pathway. The Kang *et al.* hybrids are ***unable to elicit signal transduction*** and consequent mating because they are unable to interact with the receptor (pheromone). In short, the Kang *et al.* hybrids don't work. In contrast, the hybrid Gα proteins of the instant invention not only interact with the yeast Gβγ subunit, but also interact with the receptor (*i.e.*, the heterologous G protein-coupled receptor), ***thereby permitting signal transduction***. Thus, the foregoing excerpt from Kang *et al.* is a clear teaching away from the hybrid Gα proteins of the instant invention as one of ordinary skill in the art would have no motivation to combine the reference with the other cited references. Furthermore, the failure of the Kang *et al.* hybrids to produce a detectable phenotype certainly cannot be said to provide an "expectation of success".

Applicants submit that U.S. Patent No. 5284746 does not teach or suggest the claimed invention. Moreover, the secondary reference of Kang *et al.* does not make up for the deficiencies in the primary references in that Kang *et al.* does not teach or suggest methods for producing or expressing Applicants' claimed yeast cells.

In view of the foregoing, Applicants respectfully submit that the Office Action has failed to establish a *prima facie* case of obviousness in that there is no teaching or

suggestion in any of the references relied upon by the Office Action, that would have motivated the ordinarily skilled artisan to arrive at Applicants' invention. Accordingly, Applicants respectfully request that this section 103(a) rejection be reconsidered and withdrawn.

Rejection of Claims 46, 47, and 49 Under 35 U.S.C. §103(a)

Claims 46, 47, and 49 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,284,746 and Kang *et al.* (1990) *Mol. Cell. Biol.* 10:2582-2590 further in view of Chang *et al.* (1990) *Cell* 63:999-1011. (Applicants note at the outset that claim 48, which recites a mutation in a FAR1 gene, is not specifically enumerated in the rejection.)

The Office Action, at Section 9, pages 5 and 6, sets forth the allegation that it would have been "obvious to one of ordinary skill in the art at the time the invention was made, with reasonable expectation of success, to include mutations in the FAR1 gene (as disclosed by Chang and Herskowitz) when using the assay disclosed in U.S. Patent No. 5284746, modified as taught by Kang, YS. et al." The Office Action further asserts that the motivation to combine the teachings "is provided by the teachings of Chang and Herskowitz (supra) who state that FAR1 mutations allow for the observation of pheromone-responsive transcription in dividing cells, *i.e.*, in the absence of cell cycle arrest (see par. 1, p. 1001 of Chang and Herskowitz) pheromone-responsive transcription being required to drive reporter gene expression as taught U.S. Patent No. 5284746 (see col 12)".

Applicants respectfully traverse the rejection and assert that the cited combination of references fails to establish a *prima facie* showing of obviousness.

As discussed above, the invention, as recited in claim 43, is directed to a transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, with each of the

genes being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein. Claims 46, 47, and 49 depend directly or indirectly from claim 43, and therefore incorporate all the limitations of claim 43.

Applicants submit that neither U.S. Patent No. 5284746 nor the Kang *et al.* reference teaches or suggests the claimed invention for the reasons given above with regard to the rejection of claims 43, 44, 45, 47, 50, and 51, and reiterate those reasons here. Chang *et al.* disclose the cloning and characterization of the FAR1 gene as a gene responsible for cell cycle arrest. However, Chang *et al.* does not teach the mutation of a FAR1 gene in a yeast cell containing hybrid Gα protein subunits.

To establish a *prima facie* case of obviousness "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." See M.P.E.P. §2143.

Applicants submit that the claimed invention is non-obvious over the art of record because, at a minimum, one of ordinary skill in the art would have no motivation to combine the references in the manner suggested in the Office Action, and even if one were to so combine the cited references, there would be no reasonable expectation of success because one of ordinary skill in the art would not be put in possession of the invention as claimed. Indeed, the secondary reference of Chang *et al.* does not make up for the deficiencies in the primary references in that Chang *et al.* does not teach or suggest, for example, methods for producing or expressing Applicants' claimed yeast cells.

As noted above, the Office Action sets forth the assertion that the motivation to combine the teachings "is provided by the teachings of Chang and Herskowitz (supra) who state that FAR1 mutations allow for the observation of pheromone-responsive

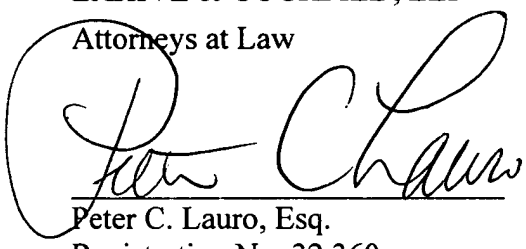
transcription in dividing cells, *i.e.*, in the absence of cell cycle arrest (see par. 1, p. 1001 of Chang and Herskowitz) pheromone-responsive transcription being required to drive reporter gene expression as taught U.S. Patent No. 5284746 (see col. 12)". However, that assertion can only come from a reading of Applicants' specification. In other words, the assertion in the Office Action is nothing more than a hindsight reconstruction of the invention based upon Applicants' teachings. Deriving the motivation from Applicants' teachings is impermissible inasmuch as M.P.E.P. §2143 makes it quite clear that the suggestion or motivation must appear either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.

In view of the foregoing, Applicants respectfully submit that the Office Action has failed to establish a *prima facie* case of obviousness in that there is no teaching or suggestion in any of the references relied upon by the Office Action, that would have motivated the ordinarily skilled artisan to arrive at Applicant's invention. Accordingly, Applicants respectfully request that this section 103(a) rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all the rejections, and allowance of all the pending claims are respectfully requested. If a telephone conversation with Applicants' attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,
LAHIVE & COCKFIED, LLP
Attorneys at Law



Peter C. Lauro, Esq.
Registration No. 32,360
Attorney for Applicants

28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: February 26, 2001

Attachment (Appendix A)

APPENDIX A

43. A transformed yeast cell comprising a reporter gene under control of a pheromone-responsive promoter, a heterologous G protein-coupled receptor gene, each said gene being under the control of a separate promoter, a mutation in a SCG1/GPA1 gene, and a hybrid Gα protein.

44. The hybrid Gα protein of claim 43 comprising yeast Gα protein sequences and heterologous Gα protein sequences.

45. The yeast cell of claim 43 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1, ste2, and ste3.

46. The yeast cell of claim 45 further comprising a mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest.

47. The yeast cell of claim 43 wherein the reporter gene is selected from the group consisting of HIS3, URA3, LYS2, CAN1, and LacZ, and the pheromone responsive promoter is FUS1.

48. The yeast cell of claim 47 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

49. The yeast cell of claim 47 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

50. The yeast cell of claim 43 further comprising a heterologous Gα subunit.

51. The heterologous G protein coupled receptor gene of claim 43 which encodes a receptor selected from the group consisting of β2 adrenergic receptor, α2-adrenergic

receptor, 5HT-1A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, and somatostatin receptor.

52. The yeast cell of claim 50 further comprising a gene mutation causing increased sensitivity to receptor activation selected from the group consisting of sst2, svg1, ste2, and ste3.

53. The yeast cell of claim 52 further comprising a mutation at a gene that permits transcriptional activation of pheromone responsive genes without cell cycle arrest.

54. The yeast cell of claims 43 and 50 wherein the reporter gene is selected from the group consisting of HIS3, URA3, LYS2, CAN1, and LacZ, and the pheromone responsive promoter is FUS1.

55. The yeast cell of claim 54 further comprising a mutation at a FAR1 gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

56. The yeast cell of claim 54 further comprising a mutation at a gene that permits transcriptional activation of pheromone-responsive genes without cell cycle arrest.

57. The yeast cell of claims 43, 44, 45 or 50 further comprising a heterologous Gα subunit.

58. The heterologous G protein coupled receptor gene of claims 43, 44, 45 or 50 which encodes a receptor selected from the group consisting of β2 adrenergic receptor, α2-adrenergic receptor, 5HT-1A receptor, muscarinic acetylcholine receptor, growth hormone releasing factor receptor, and somatostatin receptor.

Add 62